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Focus

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Quantitative HBsAg measurement as a new surrogate marker for assessment of hepatic fibrosis in HBeAg+ chronic hepatitis B

Since its discovery in 1967 [1], qualitative hepatitis B surface antigen (HBsAg) has been widely used for diagnosis of hepatitis B virus (HBV) infection. It took almost four decades until the development of an automated reliable, specific and sensitive quantitative HBsAg assay (Architect™, Abbott Diagnosis, USA) with a dynamic range of 0.05–250.0 IU/ml, and which is capable of detecting as low as 0.05 IU/ml HBsAg, corresponding to around 0.2 ng/ml [2]. Another commercially available assay with comparable properties has recently been licensed (Elecsys HBsAg II quant assay, Roche Diagnostics, USA) [3]. These assays detect the intact, wild type infectious virus as well as the two non-infectious forms of the envelope protein, including the small, spheric surface protein (produced in excess of 10^4–10^5 over the infectious virion) and the filamentous-tubular particles containing the small, middle and large envelope proteins. The rising interest of the hepatology community in HBsAg quantification is reflected in over 60 reports, which appeared since the publication of Deguchi *et al.* in 2004 [2,4–9]. Such assays have been used to study the pathophysiology, natural history, and response to therapeutic interventions in chronic hepatitis B (CHB). Indeed, HBsAg serum levels correlate with HBV replication and with intrahepatic cccDNA in HBeAg+ CHB patients. Furthermore, HBsAg levels have been shown to correlate, although not completely, with serum HBV-DNA concentration. Thus, HBsAg derived from cccDNA has been suggested as low cost marker for follow-up of HBV replication as compared to the significantly more expensive HBV-DNA assays. It should be remembered in this context that HBsAg can also be synthesized by integrated HBV-DNA into the host genome and this form of HBsAg is undistinguishable, by current methods, from cccDNA encoded envelope protein(s). Regardless of this reservation, quantification of HBsAg serum levels as a marker for viral burden and response to anti-viral therapy is progressively being used, mainly in HBeAg + CHB patients. In such patients treated with pegylated interferon with or without lamivudine, declining HBsAg levels may predict anti-HBe and the less frequent anti-HBs seroconversion. In contrast, although HBsAg levels tend to decline following seroconversion from HBeAg to anti-HBe, the correlation between cccDNA, viral load and HBsAg levels in HBeAg negative patients is unpredictable, especially in view of the abundance of defective HBV particles in such patients.

Recently Seto *et al.* have suggested a novel application for quantification of serum HBsAg for the assessment of hepatic fibrosis in HBeAg+ CHB patients [10].They studied 140 patients in Hong-Kong (65% male, median age 32.7 years) of whom 56 (40%) had ALT $\leqslant 2 \times$ ULN. Seventy-two (51.4%) and 42 (30%) had an Ishak fibrosis score $\leqslant 1$ and 87.9% were classified as in the immune clearance phase of persistent HBV infection. Patients with fibrosis score $\leqslant 1$, when compared to patients with fibrosis score >1, had significantly higher median HBsAg levels (50,320 and 7820 IU/ml, respectively, $p < 0.001$). Among patients with ALT $\leqslant 2 \times$ ULN, serum HBsAg levels achieved an ROC analysis of 0.869 in predicting fibrosis score $\leqslant 1$. HBsAg $\geqslant 25{,}000$ IU/ml was independently associated with fibrosis score $\leqslant 1$ ($p = 0.025$, odds ratio 9.042). Using this cut-off, HBsAg level in patients with ALT $\leqslant 2 \times$ ULN, positive and negative predictive values (NPP) for predicting a fibrosis score $\leqslant 1$ were 92.7% and 60.0% respectively. For an unidentified reason, HBV DNA levels had no association with degree of fibrosis established through a liver biopsy. The investigators concluded that "*Among HBeAg-positive patients with ALT $\leqslant 2 \times$ ULN, high serum HBsAg levels can accurately predict fibrosis score $\leqslant 1$, and could potentially influence decisions concerning treatment commencement and reduce the need for liver biopsy*".

In the present issue of the *Journal of Hepatology*, Martinot-Peignoux and co-workers from France have studied a larger, and ethnically more diverse cohort of 406 Caucasian, Asian, African and Mediterranean CHB patients [11], extending and confirming the preliminary observations of Seto *et al.* regarding the inverse correlation between HBsAg levels and degree of fibrosis [10]. Both studies employed an identical quantitative HBsAg assay (Elecsys®, Roche Diagnostics). However, while the report of Seto *et al.* included only HBsAg+/HBeAg+ CHB patients of unidentified genotype, the study of Martinot-Peignoux and co-workers recruited both HBeAg positive (25%) and HBeAg negative (75%) patients. Of the 406 patients, 30% were of HBV genotype E, 26% genotype A, 24% genotype D, and 11–9% of genotype B and C, respectively.

The main findings of the French study include: (1) a strong inverse correlation between HBsAg levels and degree of fibrosis. In contrast, no such correlation was present in the HBeAg negative group. Thus, HBeAg+ CHB patients with moderate or severe

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fibrosis as assessed by the Metavir score, had significantly lower serum HBsAg and HBV-DNA levels compared to patients with no or little fibrosis. (2) A strong correlation was found between HBsAg and HBV-DNA levels in the HBeAg+ group, but not in the HBeAg– group. (3) Interestingly, lower HBsAg levels and increased severity of fibrosis were greater in patients with normal ALT levels as compared to patients with elevated ALT. (4) Importantly, 50% of the overall study population with cirrhosis and 69% of the HBeAg+ cohort with cirrhosis belonged to genotype A. (5) Genotype B patients had the highest HBsAg levels. (6) Using ROC analysis, the overall ability of serum HBsAg levels to differentiate HBeAg+ patients into low (F0–F1) or moderate to advanced fibrosis (F2–F4) was calculated as 0.77 rising 0.89 in patients with normal ALT. (7) HBeAg+ patients infected with genotype B or C could be separated into moderate and severe fibrosis as compared to no or mild fibrosis, using serum HBsAg levels alone without ALT. Thus, an overall cut-off value (irrespective of ALT) for serum HBsAg levels of 3.85 log IU/ml was calculated for these genotypes at a theoretical specificity of 86% and an NPP of 100%.

Comment: the study by Martinot-Peignoux and co-workers [11] indeed confirms the association between lower serum levels of HBsAg and the presence of moderate to severe fibrosis in HBeAg+ CHB patients as initially reported by Seto *et al.* [10]. The report is adding new information generated in a relatively large cohort of patients who also underwent genotyping for HBV. An in-depth comparison between the two studies can be found in the discussion in the report by Martinot-Peignoux *et al.* [11]. At present, the mechanism, leading to a decreased HBsAg level in HBeAg+ patients with advanced fibrosis is not understood. It was hypothesized that enhanced immune clearance of HBsAg or intracellular block of HBsAg secretion may be involved in such a process [10]. Regardless of the mechanism involved, the knowledge that high HBsAg levels may predict insignificant fibrosis in HBeAg+ patients is reassuring. However, despite its putative advantage and before embracing another method for assessment of hepatic fibrosis, further validation of these data is recommended. In particular, a comparison with already available means for assessment of fibrosis (i.e., elastography) is warranted in a larger cohort of HBeAg+ CHB patients with adequate representation of the individual genotypes and ethnic groups. Finally, Tseng and co-workers have recently suggested that in HBeAg- patients, high HBsAg levels can predict disease progression [12]. This observation stands in contrast to the reports of Seto et al and Martinot-Peignoux et al [10,11]. The different role of HBsAg quantification in these two risk groups awaits further confirmation and clarification.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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